REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1-6, 9-14 and 17-21 are under examination in this application. Claims 1, 4-6, 9, 10, 12, 17-19 and 21 have been amended without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Support for the amendments can be found throughout the specification. Particularly, support for the amendment to claim 1 can be found on page 52, lines 3-4; support for the amendment to claim 5 can be found on page 7, lines 6-18; support for the amendment to claim 9 can be found on page 2, line 16; and, support for the amendment to claims 12 and 19 can be found on page 25, line 16 and on page 25 in the paragraph beginning on line 23. Claims 33 and 34 have been added to round out the scope of protection to which Applicants are entitled.

No new matter has been added by these amendments.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support is found throughout the specification and from the pending claims.

II. THE OBJECTIONS TO THE DISCLOSURE ARE OVERCOME

The disclosure was objected to because drawings were present in the specification which would be more properly placed in the drawings section. The drawings on pages 81-86 have been removed from the specification and are hereby submitted as Figures 73-77, attached hereto.

The disclosure was also objected to for containing embedded hyperlink and/or other browser-executable code. These have been removed from the text, overcoming the objection.

III. THE REJECTION UNDER 35 U.S.C. § 112, 1st PARAGRAPH, IS OVERCOME

The Application Provides an Adequate Written Description

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time of filing. The Applicants respectfully disagree. It is submitted that the present application provides an adequate written description of the claimed invention; thus, the following traverse is offered.

The lead case on the written description requirement is *In re Edwards*, 568 F.2d 1349 (C.C.P.A. 1970). The application of that case by the Federal Circuit is the state of the law on the issue. According to *Edwards*, the function of the written description requirement is to:

> [E]nsure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; to comply with the description requirement, it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him.

(*Id.* at 1351-52).

Thus, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by a skilled artisan. Applying the law to the instant facts, it is clear possession did exist at the time of filing. The invention is drawn to, *inter alia*, a novel retrotransposon, pCal, which is a member of the Tyl/*copia* group of retrotransposons.

The Office Action asserts that there is not teaching in the specification of how pCal maintains the copy number of 40-150 per host cell genome. Strain hOG 1042 has the highest number of integrated copies (10-12) and the highest level of free pCal. The unrelated strain, F16932, also shows a high free pCal level. This strain has never been mutagenized, and is a recent prototrophic clinical isolate. F16932 has six integrated copies of the element. ATCC10261 has two integrated copies, resulting in a detectable level of RNA, but no detectable free pCal on a Southern blot. Most *C. albicans* have one integrated copy and no detectable RNA transcript or free pCal DNA. In summary:

Strain	Integrated Copy Number	p Cal RNA transcript (Northern)	Free pCal DNA (Southern)
most *C. albicans*	1	-	-
ATCC10261	2	+	-
F16932	6	++	+
hOG1042	10-12	+++	++

Minus (-) indicates that there is no detection; plus (+) indicates that there is detection; multiple + indicate relative amounts of detection.

Applicants wish to point out that the high copy number as a free, linear, dsDNA molecule is, in itself, a characterizing feature of the retrotransposons of the invention. The feature of a high copy number of free dsDNA is easy to determine by anyone skilled in the art by running uncultured genomic DNA out on an agarose gel. (See Example 4, paragraph bridging pages 49 and 50.)

There are further structural features that render the retrotransposons of the invention unique. (See page 49, lines 9-22.) First, in both the free and integrated pCal, the pol and gag ORFs are in the same phase, separated by a UGA stop. This very unusual feature is shared with the related *C. albicans* Tca4. None of the other *C. albicans* retrotransposons use this method of downregulating pol, nor do any of the *S. cerevisiae* retrotransposons. Also, the 8bp/pseudoknot is found in both the free and integrated pCal; similar secondary structures are found in other retrotransposons. Finally, the four tandem repeats of GAAAAA are found in both the free and integrated pCal. They are the only retrotransposons known to have this feature, which is not present in even the related Tca4. It is respectfully submitted that the description of these features provides adequate written description for the retrotransposons disclosed in the present specification. Therefore, reconsideration and withdrawal of the Section 112, first paragraph, rejection is solicited.

IV. THE REJECTIONS UNDER 35 U.S.C. § 112, 2nd PARAGRAPH, ARE OVERCOME

Claims 1-6, 9-14 and 17-21 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Office Action found fault specifically with the phrase in claim 1, "having a copy number of between 40-150 or 50-100 copies of free DNA of itself per genome" and with the phrase in claim 5, "capable of integrating into the DNA in a genome providing a copy number of

between 40-150 or 50-100 copies per genome". Claims 1 and 5 have been amended to more clearly define the claimed subject matter.

Claims 4 and 6 recited a broad limitation together with a narrow limitation by the recitation of "fungi or yeast" and "*Candida* or *Candida albicans*". The narrow limitation has been removed from claims 4 and 6, obviating this rejection.

The term "system", deemed indefinite, has been replaced by the term "construct" in claims 10, 17 and 18. The term "retroviral-like" has been removed from claim 17.

The references in claims 9, 10, 12 and 19 to regions of DNA sequence shown in Figure 2B have been replaced by recitation of particular SEQ ID NOs. Further, the language "comprising an internal domain for receiving a nucleotide sequence encoding a desired protein flanked by two long terminal repeat regions" in claims 9 and 10 has been amended. Finally, the phrase, "particularly as seen in Figure 2B" has been removed from claim 21.

In view of the above, reconsideration and withdrawal of the Section 112, second paragraph, rejections are respectfully requested.

V. THE REJECTIONS UNDER 35 U.S.C.§102 ARE OVERCOME

Claims 1-6, 9-14 and 17-21 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Mathews *et al.* This rejection is traversed. It is respectfully pointed out that Mathews *et al.* is not a proper 102(a) reference, as it has authors that overlap with the present inventors. Therefore, Mathews *et al.* does not represent the work of "others"; a Declaration by the inventors attesting to that fact is attached hereto.

Claim 5 was rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Farman *et al.* This rejection is traversed.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

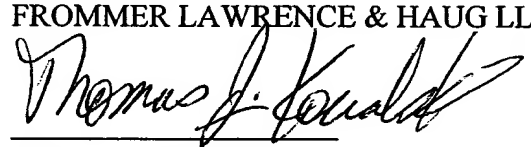
Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention. In contrast to the instant invention, the retrotransposable element, MAGGY, does not occur as a free, linear, dsDNA, and does not occur as a distinct band when uncut genomic DNA prepared from *Magnaporthe grisae* is analyzed on an agarose gel. Claim 5 includes this feature, and is thus distinguished from Farmen *et al.*

Reconsideration and withdrawal of the Section 102 rejections are believed to be in order, and such action is respectfully requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
(212) 588-0800

OIPE
AUG 1 3 2002
PATENT & TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Please amend the specification without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

On page 60, line 7:

The DNA sequence of the regions flanking the integrated copy of TCa2 was also determined (not shown). Starting about 800 bp upstream of the retrotransposon is sequence virtually identical to that of the 5' regions of the *C. albicans* CDR1 gene (Prasad et al 1995), which has been assigned to chromosome 3 [(http://alces.med.umn.edu/candida/maps/3.html)]. About 100 bp downstream is the start of an ORF that bears a strong resemblance to the 5' regions of cytoplasmic dynein heavy chain genes found in some other fungi. A *C. albicans* sequence containing an ORF that bears a strong resemblance to the central region of other fungal cytoplasmic dynein heavy chain genes has previously been assigned to chromosome 3 [(http://alces.med.umn.edu/bin/genelist LDYN1)]. These findings indicate that the cloned copy of TCa2 is located on chromosome 3, between CDR1 and a gene encoding cytoplasmic dynein heavy chain. Using PCR and primers corresponding to sequences on either side of the TCa2 integration site we were able to amplify and sequence, from hOG759, another allele without an integrated retrotransposon. This work revealed, therefore, that this locus is heterozygous for the presence of TCa2, and it also showed that the insertion of TCa2 resulted in a duplication of 5 bp (ACACG) at the integration site, as is commonly found with other retrotransposons.

On page 80, line 26:

In order to 'tag' the retrotransposon the intention was to use an inverted ('back to front') intron inserted within a reporter gene (URA3). Such an inverted intron would prevent URA3 phenotypic function unless the intron is removed from the transcript (Figure 73).

On page 82, line 8:

There is no experimental work on introns in *Candida*. So we selected one possible candidate, the very small intron (mini-intron) from the peptide transporter gene (Basrai et al 1995). This was amplified by PCR and inserted into the URA3 gene in both the forward and backward direction (Figure 74). The forward was a control to make sure the peptide transporter intron would splice. As expected, it did.

On page 83, line 6

We have now mounted this URA3/inverted intron element onto a retrotransposon plasmid putting the element into a (synthetic) Nsi1 site at the 3′ end of the coding sequence. We have also added an ADE2 element between the right LTR and the *Candida* ARS (CARS). This is summarised in Figure 75[below].

On page 84, line 1:

The plasmid is quite large and therefore not that easy to work with but it has been completed. The plasmid has been transformed into two ADE2$^-$URA$^-$ strains, one carrying a URA3 point mutation and the other a URA3 deletion (a small deletion) (Figure 76). ADE2$^+$ transformants were selected and grown at 37°C to encourage retrotransposition. Cultures were then plated on minimal medium + adenine. The plasmid is lost under these conditions and only URA$^+$ variants (retrotranspositions?) can grow. Both strains gave URA$^+$ derivatives. The URA$^-$ point mutation is reasonably stable and the URA$^-$ deletion completely so. We, therefore, are sure that these URA$^+$ variants are not revertants. They are, we believe, a mixture of retrotransposition and gene conversion. There is very little literature on gene conversion in *Candida*.

On page 86, line 1:

These should only give a product following a retrotransposition event since the intron must be removed before primer i) will work (Figure 77).

IN THE CLAIMS:

Please amend the specification without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

1. (Amended) An isolated and purified retrotransposon comprising the gag and pol ORF in the same phase and found as an extrachromosomal DNA molecule having a copy number of [between]40-150 [or 50-100 copies of]free DNA copies [of itself]per cell[genome].

4. (Amended) A retrotransposon according to claim 1 which is isolated from fungi or yeast[, including *Candida* or *Candida albicans*].

5. (Amended) A retrotransposon comprising the genetic material encoding at least one polypeptide positioned between at least two long terminal repeats,[and] wherein the retrotransposon is present at a copy number of between 40-150 free DNA copies of itself per cell, and wherein the free DNA copies are capable of integrating into the DNA of[in] a host genome[providing a copy number of between 40-150 or 50-100 copies per genome].

6. (Amended) A retrotransposon according to claim 5 which is isolated from fungi or yeast[, or *Candida albicans*].

9. (Amended) A transposable element for introducing a desired DNA sequence into the genome of a cell, having the sequence identified in SEQ ID NO: 3 comprising an internal domain for receiving a nucleotide sequence encoding a desired protein, said internal domain comprising the gag and pol ORF in the same phase and flanked by two [long] terminal repeat regions[having the sequences identified in Figure 2B].

10. (Amended) A DNA transfer construct[system] comprising:

a) a transposable element for introducing a desired DNA sequence into the genome of a cell, having the sequence identified in SEQ ID NO: 3 comprising an internal domain for receiving a nucleotide sequence encoding a desired protein, said internal domain comprising the gag and pol ORF in the same phase and flanked by two [long] terminal repeat regions[having the sequences identified in Figure 2B], said transposable element being capable of integrating into the genome of a cell in the presence of an integration factor; and

b) an integration factor.

12. (Amended) An isolated and purified retrotransposon comprising a nucleotide sequence selected from the group consisting of:

(a) SEQ ID NO: 3[The sequence illustrated in Figure 2B];

(b) A nucleotide sequence with at least 65% similarity with the LTR and POL region SEQ ID NO: 3[of Figure 2B]; and

(c) A nucleotide sequence that hybridizes under stringent conditions [of standard stringency]to SEQ ID NO: 3[the nucleotide sequence shown in Figure 2B; and

(d) A functional fragment of (a), (b) or (c)].

17. (Amended) A [retroviral-like]carrier construct[system] comprising the retrotransposon of claim 1, 5 or 12.

18. (Amended) A transformation and expression construct[system] for fungi or yeast or *Candida* comprising a retrotransposon of claim 1, 5 or 12.

19. (Amended) A nucleic acid fragment selected from the group consisting of:

(a) a nucleic acid sequence positioned between at least two [long] terminal repeats of the sequence of pCal as described in GenBank accession number AF007776;

(b) a nucleic acid sequence with at least 65% similarity with the LTR and POL region of the sequence of (a); and

(c) a nucleic acid sequence that hybridizes under stringent conditions [of standard stringency] to the nucleotide sequence of (a)[; and

(d) a functional fragment of (a), (b) or (c)].

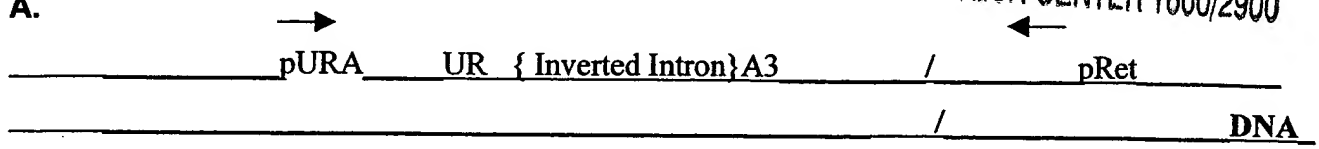
21. (Amended) A nucleic acid fragment according to claim 19 in which the nucleic acid sequence comprises two long terminal direct repeats flanking a series of genes in the order gag (group antigen), pol (polyprotein) where the pol sequence comprises an aspartic protease, an integrase and a reverse transcriptase/RNAseH[, particularly as seen in Figure 2B].

OIPE
AUG 13 2002
PATENT & TRADEMARK OFFICE

Figure 73

RECEIVED
AUG 19 2002
TECH CENTER 1600/2900

A.

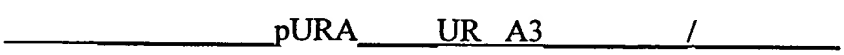


Initial DNA construct.

Transcript from URA3 promoter (pURA).

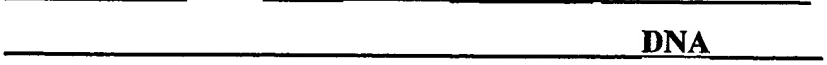
B.

(before splicing)



(after splicing)

C.



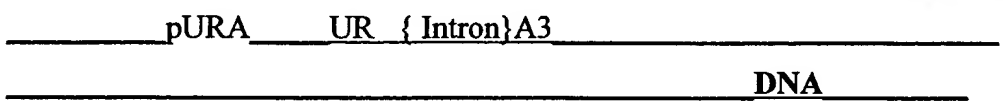
Integrated spliced construct.

OIPE
AUG 13 2002
PATENT & TRADEMARK OFFICE

Figure 74

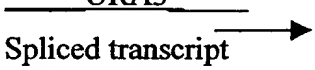
RECEIVED
AUG 19 2002
TECH CENTER 1600/2900

A.



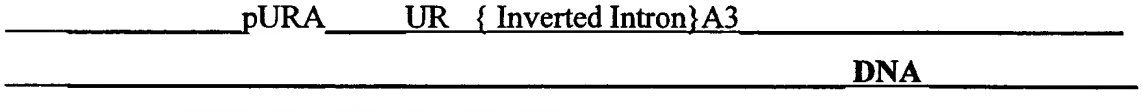
URA3 gene with forward Intron

Initial Transcript

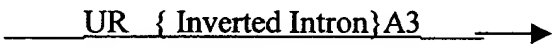


Spliced transcript

B.



URA3 gene with Inverted Intron

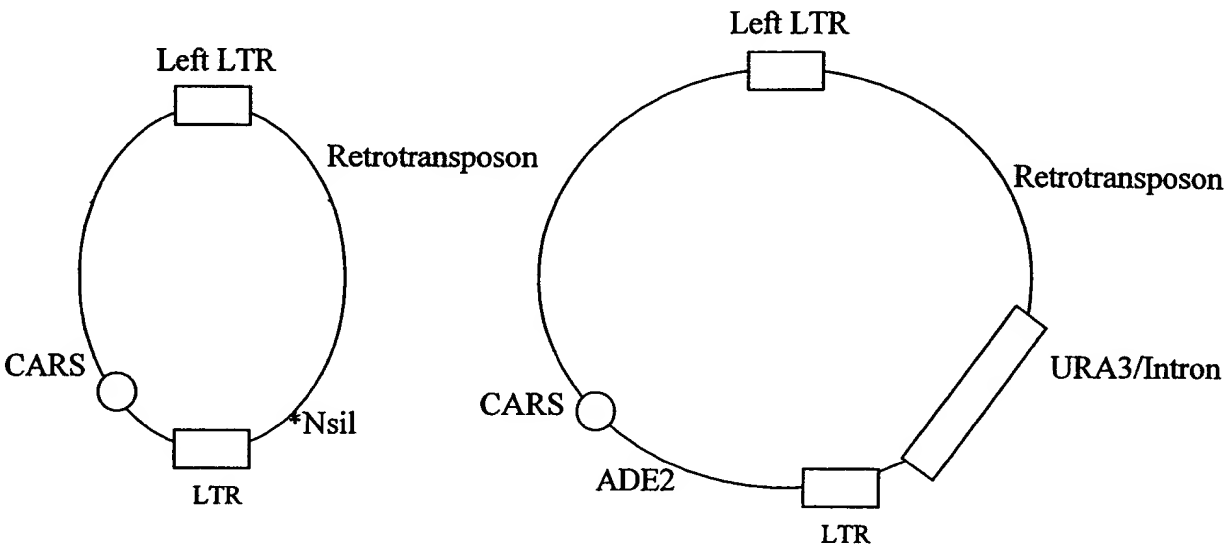


Initial Transcript (cannot be spliced)

OIPE
AUG 1 3 2002
PATENT & TRADEMARK OFFICE

Figure 75

RECEIVED
AUG 1 9 2002
TECH CENTER 1600/2900

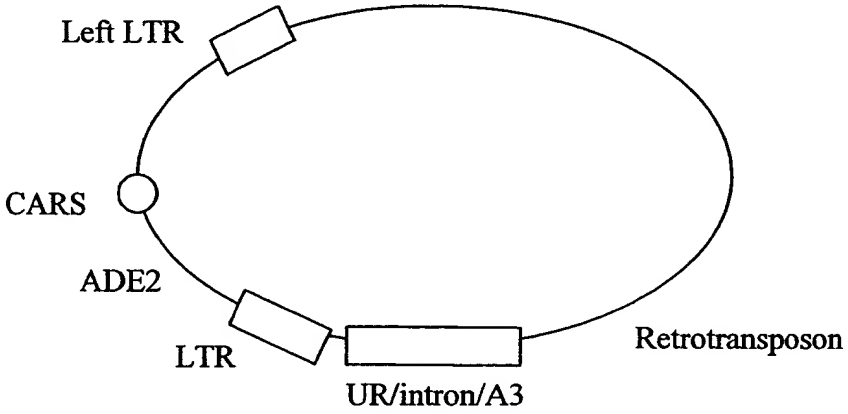


OIPE
AUG 1 3 2002
PATENT & TRADEMARK OFFICE

Figure 76

RECEIVED
AUG 1 9 2002
TECH CENTER 1600/2900

A.



B.

URΔA3 URA3Δ**(Deletion)** Homozygote

URΔA3 **DNA** with characteristic ΔSouthern pattern

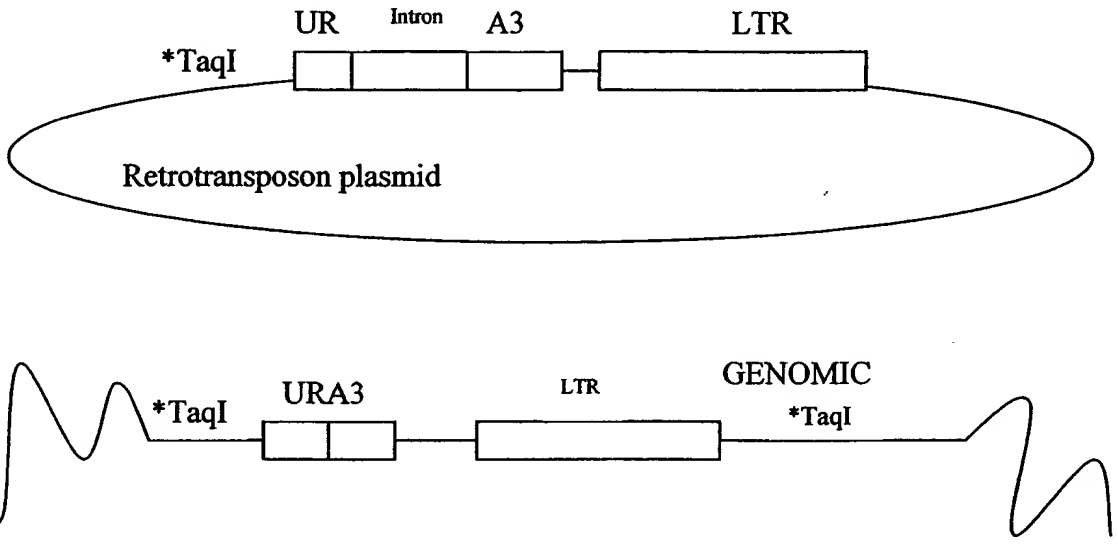
URA3+

URA3 allele due to gene conversion

OTPE JC101
AUG 1 3 2002
PATENT & TRADEMARK OFFICE

RECEIVED
AUG 1 9 2002
TECH CENTER 1600/2900

Figure 77



Integrated into genome following retrotransposition